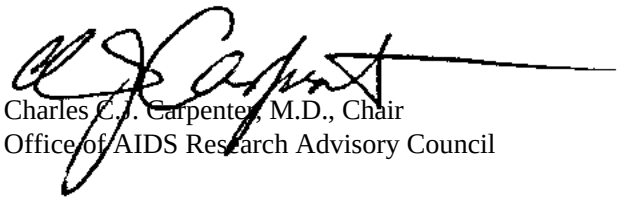
Foreword by Dr. Charles C.J. Carpenter, Chair
Office of AIDS Research Advisory Council

The Office of AIDS Research Advisory Council accepts and endorses the Report of the NIH AIDS Research Program Evaluation Task Force. This report, which was commissioned by the Office of AIDS Research Advisory Council, is the result of a comprehensive study of the entire $1.4 billion NIH AIDS research program. The year-long study was conducted by over 100 members of the AIDS and general scientific research communities under the leadership of Dr. Arnold Levine of Princeton University and co-chaired by Dr. Harold Ginsberg, Columbia University College of Physicians and Surgeons. The NIH investment in AIDS research during the initial 15 years of the epidemic has paid unprecedented dividends in elucidating key elements of the pathogenesis of this disease and in the development of basic science insights that have major implications for many other areas of biomedical research. Basic biomedical research supported by the NIH has provided the intellectual framework for the increasingly effective therapeutic interventions for this disease. At the same time, formidable challenges still remain in developing an effective AIDS vaccine.

The report makes a series of recommendations to enhance the NIH AIDS research program through more effective coordination of the endeavor. It identifies key scientific areas that warrant special emphasis. The report recommends an increased emphasis on investigator-initiated research and a reinvigoration of research efforts in vaccine and prevention research. The Office of AIDS Research Advisory Council emphasized that the implementation of the recommendations contained in this report should be a part of the ongoing evolution of the NIH's AIDS research programs. In this rapidly changing field with such vital worldwide public health implications, objective periodic evaluations of the progress and scientific opportunities are of critical importance. This report is a forward-looking document that provides a blueprint for AIDS research priorities for the next five years.



Charles C.J. Carpenter, M.D., Chair
Office of AIDS Research Advisory Council

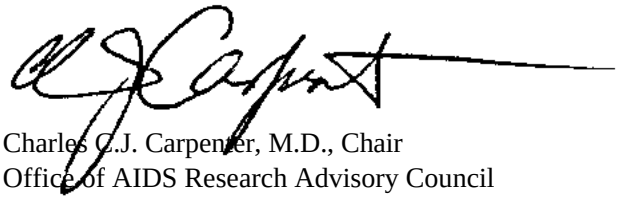
REPORT OF THE

NIH AIDS RESEARCH PROGRAM
EVALUATION WORKING GROUP
OF THE
OFFICE OF AIDS RESEARCH ADVISORY COUNCIL

Statement of Dr. Charles C.J. Carpenter, Chair
Office of AIDS Research Advisory Council
Regarding the Report of the NIH AIDS Research Program Evaluation Working Group

"The Office of AIDS Research Advisory Council unanimously accepted the Report of the NIH AIDS Research Program Evaluation Working Group today. This report is the result of a comprehensive study of the $1.4 billion NIH AIDS research program, which was commissioned by the Office of AIDS Research Advisory Council to objectively evaluate the NIH AIDS research agenda. The year-long study was conducted by over 100 members of the AIDS and general scientific research communities under the leadership of Dr. Arnold Levine of Princeton University. The investment in AIDS research made by the National Institutes of Health during the initial 15 years of the epidemic has paid unprecedented dividends in elucidating key elements of the pathogenesis of this disease and in the development of basic science insights that have major implications for many other areas of biomedical research. Basic biomedical research supported by the NIH has provided the intellectual framework for the increasingly effective therapeutic interventions for this disease and has outlined the formidable challenges that still remain in developing an effective AIDS vaccine. The Executive Summary of the Working Group outlines a series of recommendations that build on the strong scientific foundations that has emerged from this research effort.

The report makes a series of recommendations designed to further enhance the NIH AIDS research program by creating more effective coordination of the endeavor and identifies several key scientific areas that warrant special emphasis. The report recommends an increased emphasis on investigator-originated research and a reinvigoration of research efforts in vaccine and prevention research. Today, the Office of AIDS Research Advisory Council emphasized the implementation of recommendations contained in the report is a part of the ongoing evolution of the NIH's AIDS research programs. In this rapidly changing field with such vital worldwide public health implications, objective periodic evaluation of the program and scientific opportunities are of critical importance; this report is a forward-looking document that outlines AIDS research priorities for the next five years," said Dr. Carpenter in accepting this report.



Charles C.J. Carpenter, M.D., Chair
Office of AIDS Research Advisory Council
March 13, 1996

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Introduction

Fifteen years of AIDS research have begun to yield new dramatic interventions that can prevent disease, prolong health, improve quality of life, and extend survival. With the development of new, more powerful anti-HIV drugs, we have the first real chance to transform HIV disease from an inexorably fatal condition to a chronic, manageable viral infection and, in the case of children born to HIV-infected women, actually prevent many HIV infections. Great strides have been made in understanding basic aspects of the biology of HIV, and these insights lay a strong foundation for the development of even more effective therapies to treat HIV infection and new intervention strategies to prevent infection.

The present challenge for the biomedical research community is to use our newly acquired knowledge expeditiously to develop new and better therapies and to derive effective vaccines and behavioral interventions enabling us to stop the expanding devastation of AIDS and to one day eradicate the disease entirely. To guide the National Institutes of Health (NIH) in these new directions, a unique process was undertaken. A group of scientific experts from outside the Government was assembled and asked to evaluate each of the components of the current NIH AIDS research program. This review was unprecedented in its breadth and scope, due to the magnitude of the research program, which cuts across every NIH Institute and Center. The group was asked to take a broad view in assessing how these components fit together and determining whether the program as a whole is moving effectively and efficiently toward the goal of preventing and curing AIDS.

The United States funds 85 percent of the worldwide public-sector investment in AIDS research. The driving force of this research effort is the NIH, whose portfolio of AIDS and AIDS-related research has grown from a several-million-dollar investment during the early 1980s to a $1.4 billion effort today involving virtually all of the Institutes and Centers.

This report provides a blueprint for restructuring the NIH AIDS research program to streamline research, strengthen high-quality programs, eliminate inadequate programs, and ensure that the American people reap the full benefits of their substantial investment in AIDS research.

Mission and Scope of the AIDS Research Program Evaluation Working Group

In late 1994, the Office of AIDS Research (OAR) Advisory Council, chaired by Dr. Charles Carpenter of Brown University, established the AIDS Research Program Evaluation Working Group. Dr. Arnold Levine of Princeton University was recruited to lead this group of outstanding scientists and community advocates. The Working Group subsequently established six Area Review Panels to review AIDS research on Etiology and Pathogenesis; Drug Discovery; Clinical Trials; Vaccine Research and Development; Behavioral, Social Science, and Prevention Research; and Natural History, Epidemiology, and Prevention Research. Over 100 scientists from academia and industry as well as community advocates participated in these panels.

The six panels and the Working Group met regularly throughout 1995 and early 1996 to review information provided by the NIH Institutes, Centers, and Divisions (ICDs) that conduct and support AIDS research and to review budget and program information retrieved from databases maintained by the OAR and the Division of Research Grants (DRG). In addition, reviewers met with ICD Directors, key program staff, intramural and extramural scientists, and a wide variety of experts from inside and outside the field of AIDS research. Special ad hoc subpanels were convened to examine cross-cutting

issues, such as animal models, opportunistic infections (OIs), AIDS centers, complementary and alternative medicine treatments, methods to increase the number of AIDS researchers, and the optimization of community involvement in the NIH AIDS research program.

Each Area Review Panel identified the scientific priorities within its area, evaluated the current research portfolio, and developed recommendations to improve, enhance, and streamline AIDS research. The individual Area Review Panel reports document their specific evaluations and detailed recommendations. The Working Group took a broader view, identifying key issues and developing major recommendations that span scientific areas and underpin the overall NIH AIDS effort. In some cases, the Working Group report reflects a consensus position that reconciles somewhat divergent conclusions found in individual Area Review Panel reports.

Scope of the HIV Pandemic

Recitations of the numbers of cases of AIDS and HIV infection cannot possibly convey the magnitude of human suffering experienced by millions of infected individuals and their loved ones around the world. The HIV/AIDS pandemic holds the potential to become one of the most costly and debilitating scourges of humankind. AIDS kills people in their most productive years. In the United States and other countries, AIDS is the leading cause of death among young people.

The World Health Organization estimates that, worldwide, nearly 20 million men, women, and children already have become HIV-infected; 4.5 million of these individuals have progressed to AIDS and 2.5 million have died. Nearly 10,000 new infections occur each day. Over 5 million children under 10 years of age will be orphaned as a result of the death of their parents from AIDS. The increasing magnitude of the AIDS pandemic will result in unprecedented levels of personal suffering, high direct costs of medical care for infected persons, reduced economic output in many countries struggling for economic growth, and other substantial costs to society.

In the United States, the demographics of the epidemic are changing, increasingly resulting from heterosexual transmission, affecting greater numbers of women, and disproportionately affecting persons from racial and ethnic minorities.

Accomplishments of AIDS Research

The signal successes of AIDS research, many of them made possible by NIH support, include the following:

- The identification of the etiologic agent, HIV, and the elucidation of the natural history of HIV disease including the identification, isolation, and characterization of HIV, its gene products, key viral proteins, and susceptible host cells and organs; the elucidation of the HIV life cycle; the description of the natural history of HIV disease and the development of prognostic laboratory markers such as $CD4^+$ T cell levels and plasma virus load, which can now be determined through recently developed assays.

- The development of strategies to prevent HIV transmission, including the use of sensitive and specific tests to diagnose HIV infection and to effectively screen and protect the nation's blood supply; behavioral interventions to reduce sexual transmission; interventions to reduce parenteral

transmission among injection drug users (IDUs); and the use of AZT to reduce maternal-fetal HIV transmission.

- The clinical and basic research advancements that have fostered the development of therapeutic interventions to prolong and improve the quality of life of HIV-infected individuals, including the development of two classes of antiretroviral agents (inhibitors of HIV reverse transcriptase and HIV protease) and more effective and less toxic regimens to prevent and treat many of the most common AIDS-related infections and malignancies.

Structure and Growth of the NIH AIDS Research Program

In response to the emergence of the HIV/AIDS epidemic in the early 1980s, the NIH received a major infusion of funds appropriated by Congress earmarked for AIDS research. Most of the earliest AIDS research was conducted by the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Diseases (NIAID), which by 1985 was the lead Institute sponsoring AIDS research. The challenges posed by AIDS, however, exceeded the mission of any individual Institute. AIDS is a multisystem and multiorgan disease, involving malignancies, OIs, and neurological, gynecological, ocular, oral, dermatological, and gastrointestinal complications. It affects people across the life span from infancy to old age. Behavioral and biomedical interventions are required to prevent new infections. Consequently, virtually every ICD became involved in conducting or supporting AIDS research.

This burgeoning effort required coordination. The OAR was established in 1988 for this purpose. However, its limited authority hindered its ability to fully coordinate the diverse AIDS-related research carried out by the ICDs. In turn, this limited the ability of NIH to set overall scientific priorities, manage the vast research endeavor, and evaluate and assess progress against the disease.
One solution to coordinate this diverse research might have been to establish a new Institute dedicated to AIDS research. However, such an action would have involved considerable disruption of ongoing science. It became clear to many concerned scientists, legislators, and community representatives that greater authority was needed to strengthen the OAR so that it would function as an "Institute without walls." Congress subsequently passed the NIH Revitalization Act of 1993, which significantly strengthened the OAR, providing it with the authority to plan, coordinate, and evaluate AIDS research, to set scientific priorities, and to determine the budgets for all ICD AIDS research. The Working Group and Area Review Panels unanimously recognize and endorse the crucial need for a continued strong and viable OAR to provide the overall scientific leadership and coordination of the NIH AIDS research program.

Cross-Cutting Themes and Recommendations

While much of the NIH AIDS research portfolio is of the highest quality and relevance, the Area Review Panels and the Working Group were convinced that there is a need for improved focus and better coordination between ICD research programs. Many specific needs and recommendations were identified in the individual panel reports; however, a number of common themes emerged:

- The need for ongoing scientific oversight and review by non-Government scientists. The Working Group commends NIH for sponsoring this evaluation and urges it to increase the involvement of non-Government scientists in review and oversight of all important NIH programs, including AIDS research.

- The need for better integration and coordination of AIDS research among the ICDs and between intramural and extramural researchers. This will require a strong and viable OAR.

- The need for intensified collaboration with the pharmaceutical and biotechnology industries to develop new classes of drugs as well as safe and effective vaccines.

- The need for a rededication to basic research initiatives. This will require a redistribution of funds and the recruitment of high-caliber investigators to AIDS research. Specific initiatives should focus on HIV pathogenesis, viral gene-coded products and their functions; novel interventions that interfere at various stages of the viral life cycle; the human immune system and its response to HIV infection; and basic biology and pathogenesis of OIs and malignancies.

- The need to intensify and integrate research to prevent HIV transmission, including its biomedical and its behavioral aspects.

- The need for continued and enhanced HIV community involvement in AIDS research. Among the unique features of NIH's AIDS research effort is that HIV community advocates are involved at all levels of the research infrastructure, including reviews such as this one. AIDS community representatives play a critical role in making research more accessible to communities affected by HIV and more responsive, relevant, and acceptable to target populations. The Working Group urges NIH to continue to support HIV community involvement in AIDS research programs.

Because the OAR has the authority to plan and coordinate NIH AIDS research, the Working Group charges the OAR to rapidly develop and implement an action plan to address the specific needs identified by this evaluation. We also call on the NIH Director, the OAR Director, and the ICD Directors to work with the research community in a collaborative spirit to expedite the implementation of the proposed recommendations.

I. INVESTIGATOR-INITIATED RESEARCH

Increase support for and improve peer review of investigator-initiated research

The nurturing of novel research approaches, concepts, and directions is essential for progress against AIDS. Research innovation and productivity require adequate levels of funding for meritorious projects, stability of grant support for productive, experienced AIDS researchers, and an ongoing infusion of new investigators to the AIDS field. The Working Group believes that the success of the NIH's AIDS research effort absolutely depends on high-quality, informed peer review of research proposals.

Support for Investigator-Initiated AIDS Research

The Working Group believes that there is no better way to enhance the diversity and productivity of research approaches than to actively encourage and support peer-reviewed, investigator-initiated and driven research. This principle holds true for all areas of AIDS research including the basic sciences, the clinical sciences, the epidemiological sciences, and the behavioral sciences. However, the pool of funds dedicated to support investigator-initiated AIDS research is proportionally less than those typically devoted to other NIH-sponsored research programs. Indeed, in 1994 only about 20 percent of NIH AIDS extramural research expenditures could be classified as unsolicited investigator-initiated research, as compared with approximately 50 percent for non-AIDS projects. Since the beginning of the AIDS epidemic, the ICDs have tended to manage AIDS research with more direct scientific control than other research portfolios. Requests for applications (RFAs), collaborative agreements, and contracts were heavily utilized as research support mechanisms. Earlier in the epidemic, when the available level of knowledge was less and the community of researchers involved in AIDS research was smaller, this was an effective approach to establish the infrastructure and preliminary knowledge base for nascent AIDS research efforts. However, given the maturation of the field and the nature of the contemporary research needs, the continuation of this approach represents an impediment to progress.

A primary consequence of the current distribution of funds is that the resources available for unsolicited investigator-initiated research are simply insufficient. Proposals that ultimately receive funding most often do so only after multiple submissions for review. Delays resulting from multiple review cycles inevitably slow progress that can be made against the disease. Another negative consequence of the intense competition for research dollars is that many investigators are reluctant to submit novel or innovative proposals. Furthermore, the tight competition for grants has led the Initial Review Groups (IRGs) to heavily favor applications containing extensive preliminary data. While this is an important criterion by which to evaluate the merit of grant applications, it represents a major barrier to attracting new investigators to the field of AIDS research.

To remedy this situation, the Working Group recommends a substantial increase in the support for investigator-initiated AIDS research across the NIH.

Recommendation

I.1 The proportion of the NIH AIDS research budget allocated to support unsolicited investigator-initiated research should be approximately doubled.

The Working Group is aware that this increase may result in different paylines for AIDS and non-AIDS research. The Working Group has determined that there are funds allocated for AIDS research that are being used to support both intramural and extramural research that is only peripherally related to AIDS. Redirection of such funds will be required to implement this recommendation. The Working Group appreciates that such redirection of funds will require time and careful planning.

Linkage of Peer Review Groups with OAR Scientific Priorities

The OAR is responsible for the development of an annual plan for NIH-sponsored AIDS research that sets scientific priorities. The development of this plan, which involves input from ICDs and from a wide range of extramural scientists, is an essential function. Similarly, the independent peer review mechanism used to judge scientific accomplishments and novel ideas is the most effective means to support high-quality research. However, there are, at present, no effective means to link the AIDS research priorities identified by the NIH Plan for HIV-Related Research to the consideration of competing research grant proposals by the peer review groups. The IRGs and the DRG should be better informed of the scientific priorities for AIDS research and should consider these priorities in their review of grant proposals for AIDS and AIDS-related research. To accomplish this goal, the Working Group recommends that:

Recommendations

I.2 Selected members of AIDS-related IRGs should participate in the OAR's process for setting research priorities. As an integral part of the IRG process, these individuals, in concert with DRG and OAR staff, should familiarize their IRG members with the OAR- and ICD-defined AIDS research priorities.

I.3 Scientific Review Administrators of AIDS-related IRGs should be included as members of the OAR Coordinating Committees corresponding to their area of expertise.

I.4 The OAR, in concert with the ICDs, should inform the ICD advisory bodies and councils of the NIH AIDS research priorities as outlined in the NIH Plan for HIV-Related Research.

I.5 The OAR should develop a strategy to distribute the NIH Plan for HIV-Related Research to the scientific community and other interested parties.

I.6 AIDS-related grant proposals should include a discussion of how the proposed investigation relates to the research priorities detailed in the NIH Plan for HIV-Related Research.

Although improved linkages between AIDS research priorities and IRG review is needed now, it will become increasingly important in the future, particularly as increases in funding for investigator-initiated research are realized. It must be emphasized that this recommendation is not an attempt to interfere with

the independent judgment of scientists or of IRGs. Rather, it is meant to encourage better coordination of scientific goals.

Quality, Scope, and Flexibility of AIDS-Related IRGs

The peer review process is central to the success of the entire research endeavor. It must be of the highest quality. The paramount consideration in achieving expert peer review is the scientific expertise of the members of the IRGs. Scientific expertise can be defined through previous record of scientific accomplishment and knowledge of the field relevant to the review. The Working Group became aware of numerous instances where the IRG process unfortunately appears to have failed to identify the most promising research projects. The Working Group believes that these failures were primarily due to limitations in the breadth, depth, or expertise of the membership of certain AIDS-related IRGs. These limitations seem to be the result of a number of factors, including constraints placed on DRG with respect to choosing IRG members, the limited enthusiasm that many members of the extramural scientific community may feel for service on IRGs in an environment where so few grant applications are funded, and the absence of an aggressive campaign on the part of the NIH and DRG to recruit expert scientists to serve on IRGs. The Working Group strongly believes that these limitations must be remedied.

Recommendation

I.7 It is critical that the DRG work with OAR and the ICDs to provide IRGs with high-calibre, mature, and diverse scientists and clinicians. DRG should investigate possible mechanisms to ensure high-quality reviews responsive to the changing scientific issues. Such mechanisms might include working with learned societies to identify distinguished scientists with a broad range of expertise to serve on IRGs, making greater use of voting *ad hoc* members, and exercising flexibility on the term limits for IRG participation.

AIDS research is continually evolving, so that areas of scientific emphasis will inevitably change over the next 5 years. There likely will be increased opportunities and needs in the future for basic, clinical, epidemiological, and behavioral scientists to collaborate in multidisciplinary studies. To expertly evaluate these multidisciplinary approaches and their translational research opportunities, it will be essential that IRGs include appropriate expertise in basic, clinical, and behavioral research. DRG should select members of IRGs and review panels with broad scientific scope and expertise to ensure that meritorious new directions and ideas are approved for funding. To support and maintain the highest quality of AIDS research and to identify promising new research directions, the Working Group recommends that:

Recommendation

I.8 DRG should be responsive to the evolving character of AIDS research and modify IRG composition or define new IRGs as needed. The Working Group believes that the existing AIDS-related IRGs should be redefined and reconfigured to reflect the current scientific priorities for AIDS research, particularly as they relate to vaccine and prevention science research needs.

Recruiting New Investigators to HIV/AIDS Research

It is critical that the NIH actively encourage exceptionally creative and productive individuals to devote at least a portion of their research effort to HIV/AIDS-related areas. A number of factors may have contributed to limited success in attracting many expert investigators to AIDS research in the past. These factors include concerns about working with infectious agents, unfamiliarity with the central scientific issues in AIDS, the perception that the field was insufficiently mature to support very focused investigations, the daunting complexity of the disease process, a lack of understanding of the human immune system and of tools to study it in detail, and the often public and contentious nature of the earlier AIDS research effort. Many of the barriers have lessened significantly over the past decade. Although provision of adequate funding to investigator-initiated research is, as discussed earlier, a necessary component of a program to attract new investigators to AIDS research, it is not the only remedy that is needed. The NIH must ensure that the remaining obstacles are addressed as well.

In the current NIH funding environment, it is very difficult for researchers who are just beginning their independent scientific careers to compete against more established investigators for funding. As the financial constraints on universities and academic medical centers continue to mount, new investigators are under increasing pressure to gain independent support rapidly. Delays in obtaining research support or the inability of attracting sufficient levels of funding to establish an independent research program can result in either the loss of a junior investigator's position or redirection of his or her efforts to teaching, service, or clinical responsibilities.

The NIH has been successful in recruiting investigators to understudied areas of science in some instances. The Working Group identified several features that are likely to be important to achieve such success in the area of AIDS research. Key among them are the quality and dedication of NIH staff involved in program initiation and oversight, and the involvement of the extramural scientific community in identifying research needs and opportunities. The Working Group recommends an active program to recruit outstanding new investigators to AIDS research.

Recommendations

I.9 Given the crucial importance of training for the research enterprise, the OAR should establish a Coordinating Committee on Training and Infrastructure, with the same responsibilities as other OAR Coordinating Committees.

I.10 OAR Coordinating Committee on Training and Infrastructure should review the NIH Plan for HIV-Related Research and address a wider range of NIH training mechanisms (such as the K awards, supplements, and predoctoral research opportunities). The Plan should include strategies for the systematic outcome evaluation of training awards.

I.11 Innovative mechanisms to provide short-term (2-3 year) support of young investigators at levels sufficient to initiate quality research programs should be developed.

1.12 Many investigator-initiated research grants in areas unrelated to HIV/AIDS objectives, held by distinguished senior scientists, generate findings that may be relevant to questions in AIDS research. To encourage these laboratories to explore AIDS-related avenues of research, a program should be established that offers supplemental funding to support postdoctoral fellows or graduate students to carry out AIDS-related research.

I.13 NIH should develop programs for AIDS-related research training explicitly tailored and targeted to ethnic minority individuals, primarily at the postdoctoral level. Rather than simply supplementing existing grants, these programs should involve collaborative mentoring activities in research projects defined by the minority scientists. Programs should include intense and long-term mentoring and support in the NIH grant application process. A criterion of evaluation of these programs should be the number of new NIH-funded principal investigators (PIs) of ethnic minority background.

I.14 OAR should investigate the possibility of extending the AIDS Loan Repayment Program (LRP) to forgive student loan debts for postdoctoral fellows working in AIDS research outside of the NIH intramural program.

II. AIDS VACCINE RESEARCH

Establish a restructured trans-NIH vaccine research effort

The development of a safe and effective vaccine to prevent HIV infection is among the highest priorities for the AIDS research effort. Yet, vaccine research historically has received less funding and attention than other areas of AIDS research. Although this may have been justifiable in the past, the continued spread of the HIV epidemic and recent advances in our knowledge dictate a reassessment of priorities and a restructuring of the NIH vaccine initiative.

In many developing nations, vaccines may be the only cost-effective way to prevent transmission and control the pathological consequences of HIV infection. Despite the urgent need, efforts to develop an HIV vaccine candidate that is likely to be highly effective have been unsuccessful to date. These efforts have been impeded by the lack of a good animal model for HIV challenge studies and our failure to identify specific correlates of immune protection, as well as other factors. However, dissection of immune responses from animals protected by vaccination or studies of individual humans who appear able to control HIV replication and possibly resist infection may provide new insights for vaccine development. While the course and time to an effective AIDS vaccine cannot be predicted, there can be no question of the importance of the effort.

The Working Group and the Vaccine Area Review Panel concluded that only with reinforced effort and commitment will a vaccine against HIV-1 be attainable. Successful development of an effective vaccine to prevent HIV-1 infection will require major investments in fundamental human immunology and vaccine biology to derive new and more potent vaccine approaches. Strategies also are needed to identify and prepare promising candidate vaccines for clinical trials and to move them rapidly, when warranted, into full-scale efficacy trials.

The Working Group recommends the creation of a restructured, trans-NIH vaccine program with centralized leadership to mobilize and focus the necessary resources to expeditiously pursue these objectives. Critical to the success of this initiative is its organization and leadership structure. The Working Group also believes that the NIH has an indispensable role in coordinating this vaccine effort with those of other Government agencies, of industry, and of international organizations.

Recommendation

II.1 The entire AIDS vaccine research effort of the NIH should be restructured. A trans-NIH vaccine program should be established with leadership and oversight provided by distinguished, non-Government scientists.

An AIDS Vaccine Research Committee (AVRC), chaired by a distinguished non-Government scientist, should be created to provide leadership, direction, and oversight to a comprehensive AIDS vaccine effort, spanning all ICDs. This effort should be established as an independent Center or Division administratively located in NIAID. Day-to-day operations of the unit should be the responsibility of a scientific and administrative expert. The composition of the AVRC should include a majority of members who are outstanding non-Government scientists with appropriate expertise; representatives of ICDs with major vaccine programs; and a representative of the OAR. Members of the AVRC should be jointly appointed by the Directors of NIH, OAR, and NIAID.

Coordinated direction across ICDs and between intramural and extramural investigators is necessary to achieve effective planning and implementation of strategies to rapidly exploit new advances. In addition to facilitating the development and evaluation of HIV vaccines, this initiative should stimulate the integration of basic research advances in immunology and vaccine science that could energize the development of new vaccines for a wide range of infectious diseases, including microorganisms that cause OIs.

Recommendation

II.2 A National AIDS Vaccine Task Force (NAVTF), chaired by the Director of OAR, should be established in the White House Office of the National AIDS Policy, with responsibility for coordinating all Government-sponsored vaccine programs.

This Task Force would integrate Government-sponsored vaccine research and development efforts of all U.S. Government agencies and coordinate them with those of pharmaceutical and biotechnology organizations, private agencies, other nations, and international organizations.

NIAID HIV Vaccine Efficacy Trials Network (HIVNET)

HIVNET was established in 1993 as a network of domestic and international sites to support primarily trials of promising AIDS vaccine candidates but also to test nonvaccine biomedical and behavioral interventions. The most important accomplishment of HIVNET to date is its success in recruiting large numbers of individuals at high risk for HIV transmission into cohorts for baseline studies. The program is gathering data on risk and incidence of HIV infection and willingness to participate in future vaccine trials, as well as evaluating consent procedures. In the absence of testable vaccine candidates, the current agenda for the HIVNET program involves continuing baseline measurements and implementing nonvaccine studies that include other prevention interventions—both biomedical and behavioral—that will be important adjuncts to the vaccine initiative.

The Working Group acknowledges the potential value of the seronegative cohorts that have been established in HIVNET for identifying newly infected individuals and for testing biomedical and behavioral interventions designed for prevention of HIV transmission. However, efforts to integrate behavioral interventions within the existing HIVNET program have not yet been fully successful. Such efforts have been impeded both by a lack of appropriate expertise in behavioral and social science research and by the Master Contract mechanism, which limits the access of potential subcontractors who have such expertise. The Working Group found that because the principal mission of HIVNET has been vaccine preparedness, it is not obvious that it has the intrinsic expertise or infrastructure to move effectively beyond this mission on a broad scale. Moreover, with a potential vaccine candidate currently being evaluated within the AIDS Vaccine Evaluation Group (AVEG) for possible efficacy studies beginning in 1998, it is not clear how existing studies of nonvaccine interventions would be affected if a vaccine candidate were available for trial or, alternatively, how these intervention studies will impact potential vaccine trials. Finally, it can be argued that the Master Contract mechanism may not be optimally conducive to an effective leadership structure within HIVNET, or to the ability of NIAID to manage this program.

Because of the significant amount of resources committed to this effort and the complexity of the scientific issues to be addressed, the Working Group believes that a comprehensive plan for HIVNET's

activities must be developed. Strong scientific input from other ICDs is needed, particularly in the areas of behavioral and biomedical prevention studies. Furthermore, because HIVNET is a broader prevention research program, it should not be categorized, budgeted, or evaluated as strictly a vaccine development initiative.

Recommendation

II.3 NIAID, in partnership with other ICDs with complementary expertise, should promptly develop a comprehensive plan for HIVNET's organization, Governance, research, and funding. This plan should be reviewed in 1996 by a joint OAR/ICD-convened panel of extramural experts in behavioral, social, epidemiological, prevention, pathogenesis, and treatment research as well as vaccine research. If reviewers determine that there are significant deficiencies in the plan, funds could be released for retargeting to other essential areas of AIDS research.

III. RESEARCH ON THE HUMAN IMMUNE SYSTEM

Augment research efforts to better understand the human immune system

There is a critical need for a greater understanding of the human immune system. Illumination of the intricacies of this system holds the keys to developing a successful vaccine to prevent HIV infection and for designing more effective therapies to limit immune system damage and to restore functional immune responses in HIV-infected persons. Great progress has been made in immunology research over the past few decades, yielding fundamental insights into the pathogenesis of infectious diseases, autoimmune diseases, and cancer. Progress has been built, in many instances, on a foundation of basic knowledge derived from the study of the mouse immune system. Study of the mouse immune system has been greatly facilitated by the availability of strains of inbred, transgenic and 'gene-knockout' mice. Insight into the function of the immune systems of humans and nonhuman primates has progressed more slowly, largely due to their greater complexity and less experimentally tractable nature. Unfortunately, simple translation of results from the mouse immune system to immune systems of primates may prove to be very misleading. The study of HIV/SIV immunology in human and primate models is underrepresented in the scientific portfolio of the NIH. Many of the most capable immunologists have not committed major efforts to AIDS research. Research on the immune systems of uninfected, and HIV-infected humans and SIV-infected primates must be established as a high priority for the NIH. To focus attention on HIV/SIV immunology and actively engage talented immunologists in AIDS research, the Working Group recommends:

Recommendations

III.1 OAR should convene a series of workshops of expert immunologists to develop a plan to accelerate progress in understanding the following:

- **The basic biology and development of human immunocompetent cells and of the unique aspects of the physiology of the human immune system.**
- **How HIV or SIV perturbs the human or primate immune system to impair the function of and destroy immunocompetent cells.**
- **Why normal replacement mechanisms are unable to restore a functional immune system in infected individuals.**
- **Why normal host defenses are unable to ultimately contain HIV infection.**

III.2 NIH should increase support for research of the human immune system by traditional mechanisms of investigator-initiated research and intramural projects.

III.3 NIH should facilitate interactions between basic immunologists and AIDS researchers through consortial approaches. Anticipated benefits of the consortial mechanism include overcoming basic immunologists' unfamiliarity with AIDS research and concerns about working with infectious agents; facilitating the exchange of ideas, techniques, reagents, and personnel; and increasing the likelihood that postdoctoral fellows enter AIDS research.

IV. HIV PREVENTION SCIENCE RESEARCH

Develop a comprehensive HIV Prevention Science Agenda

As the AIDS epidemic continues to spread into new communities in the United States and globally, primary prevention of new HIV infections must be a high priority. As of FY 1994, only about 6.5 percent of the total NIH AIDS research budget was devoted to nonvaccine primary prevention-intervention research.

A major goal for NIH should be to develop an HIV Prevention Science Agenda that is coordinated, comprehensive, and includes and combines biomedical, behavioral, and social interventions. HIV prevention science at NIH should be tied closely to basic sciences and should offer practical, evidence-based strategies for public health implementation.

An ideal comprehensive HIV prevention strategy includes three components: behavioral and social interventions, biomedical technologies (e.g., sexually transmitted disease treatments, topical microbicides, condoms, sterile needles and syringes, and antiaddiction medications), and vaccines, integrated where appropriate into a "combination" approach analogous to anti-HIV combination therapy. The priority given by the Working Group to vaccine development is described elsewhere in this document (See II above). Therefore, this section highlights the priority of the biomedical and behavioral approaches. The Working Group advocates coordination among all three components.

Appropriate and effective prevention strategies require the organization and application of fundamental knowledge in natural history, epidemiology, and behavioral and social sciences into a coordinated and effective plan. Such a plan should articulate research and intervention strategies that include biomedical, behavioral, and social approaches. Led by the OAR, it should begin with the coordination of activities across NIH, and then be coordinated with plans of other U.S. agencies and those of other countries. The goal of this HIV prevention science plan will be to identify and implement the most promising methods for preventing sexual, parenteral, and perinatal transmission.

Coordination of a Comprehensive HIV Prevention Agenda

Three steps can be taken now to promote the coordination and visibility needed for an HIV prevention science agenda: (1) an ongoing HIV Prevention Science Advisory Committee convened by and reporting to the Director of the OAR; (2) an HIV Prevention Science Coordinator charged with coordinating the implementation of the NIH HIV prevention science agenda; and (3) an IRG devoted to HIV prevention science proposals.

The HIV Prevention Science Advisory Committee should be co-chaired by a behavioral scientist and a biomedical scientist and include distinguished non-Government scientists and appropriate representatives from OAR and the ICDs with major research interests in these areas. The Committee should advise the OAR Director on the development and implementation of the HIV Prevention Science Agenda and on the coordination of its agenda with the AIDS vaccine initiative.

Scientific Opportunities and Priorities

The following high-priority scientific opportunities in the prevention science area would require an infusion of new funds.

1. Studies testing the utility of combined biomedical, behavioral, and social interventions in reducing sexual, parenteral, and perinatal transmission of HIV.

2. Domestic and international studies testing the efficacy of joint behavioral and biomedical strategies for combined control of HIV and other sexually transmitted diseases and combined control of HIV and other adverse health consequences of injection drug use (IDU).

3. Studies of the impact of social interventions, e.g., community-level interventions, legal or policy changes, on HIV risk behaviors and transmission.

4. Research on primary prevention of HIV transmission from the HIV-infected to the HIV-uninfected, with the transmission behavior of the HIV-infected person being the outcome measure.

5. Studies on prevention services delivery.

Recommendations

IV.1 NIH, acting through the OAR, should develop a coordinated and comprehensive Prevention Science Agenda that includes and combines biomedical, behavioral, and social interventions. This agenda should begin with an NIH-wide plan that then is integrated where possible with similar plans at the Centers for Disease Control and Prevention (CDC) and other relevant Federal agencies.

IV.2 NIH should convene an HIV Prevention Science Advisory Committee reporting to the Director of OAR.

IV.3 OAR should appoint an HIV Prevention Science Coordinator charged with coordinating the implementation of the Prevention Science Agenda.

IV.4 NIH IRGs for the review of AIDS research grants should be reconfigured to include one with appropriate expertise in and responsibility for HIV prevention science proposals (including cross-disciplinary studies).

V. CLINICAL TRIALS

Integrate all adult clinical trial programs into a single network

Historically, the AIDS clinical trials effort attempted to respond to a diverse set of needs and constituencies by forming several trials networks. NIAID, which is the primary sponsor of NIH AIDS clinical trials, has a number of extramural programs including the adult and pediatric AIDS Clinical Trials Groups (ACTGs), the Community Programs for Clinical Research on AIDS (CPCRA), the Division of AIDS Treatment Research Initiative (DATRI), and the Strategic Program for Innovative Research on AIDS Therapy (SPIRAT). Other Institutes sponsor additional clinical trial efforts, including the National Eye Institute (NEI) Study of the Ocular Complications of AIDS (SOCA), the National Institute of Neurological Disorders and Stroke (NINDS) Neurologic AIDS Research Consortium, units that are part of the National Institute of Child Health and Human Development (NICHD) pediatric ACTG, and the NCI AIDS Malignancy Consortium (AMC). There also are substantial intramural trials efforts in NIAID and NCI.

Adult AIDS Clinical Trials

Early extramural efforts, particularly at NIAID and NICHD, were highly directed by Institute staff. While this was appropriate when the first program was created in 1986, the rapid maturation of the investigator community has obviated the need for continued strong direction from NIH. Recent changes in the scientific leadership and organizational structure in the ACTG and CPCRA appear to be moving in the right direction; adequate time must be allotted to evaluate the impact of these changes. In some instances, ICDs with an organ system or single disease entity focus have structured independent clinical trials programs, such as SOCA and AMC. While a sharp focus and specific expertise are brought to such efforts, the resultant trials often fail to take into account the multisystem nature of HIV infection and AIDS. Other Institutes have confined their clinical trials support to conducting subspecialty studies to exploratory, investigator-initiated studies (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK]) or to support neurological trials within the ACTG (NINDS).

There has been overlap and, in some instances, unnecessary competition between these diverse programs that are funded by different Institutes with different self-defined missions. The scientific productivity of the independent clinical trials efforts has been quite variable, as has been the level of support and enthusiasm from the funding Institutes. For example, DATRI is viewed by the Working Group to be an unsuccessful effort, with inadequate scientific input from extramural investigators and limited productivity. Coordination of efforts to achieve shared research goals, including exchange of ideas and the ability to share data, has been difficult at best, even when programs have been managed by the same Institute staff. Attempts at collaborative research between programs have been hampered by the lack of standardized databases. Similarly, the lack of an organized repository for pathogens and clinical specimens from well-characterized participants in trials has inhibited collaboration with basic scientists and epidemiologists.

The Working Group believes that all NIH-sponsored clinical trials efforts should be held to the highest standards for productivity and scientific excellence. Programs that fail to meet these standards should be improved or eliminated. To best address the present and future needs for therapeutics research in AIDS, the Working Group recommends:

Recommendation

V.1 A single integrated adult clinical trials network should be created with primary sponsorship from NIAID and ancillary funding from other Institutes involved in clinical trials.

In this integrated network, scientific leadership should be provided by extramural investigators, with support from Institute staff. This proposed network should include a broad range of potential sites and investigators with various levels of expertise and scientific capability. It would replace the current ACTG, CPCRA, DATRI, and possibly SPIRAT programs under the auspices of the NIAID.

This integrated network is envisioned as one with concentric layers of research expertise and capability. Direct funding is required for the following essential elements: an operations office that supports the central administrative and scientific leadership of the group; a statistical center; the capacity to perform sophisticated virologic and immunologic assays and to continue development of new assays; and a core group of investigators/sites that can design and perform Phase I/IIA and proof-of-concept studies, which require intensive patient and laboratory monitoring. Also needed is a larger number of investigators who can perform complex Phase IIB/III trials requiring intensive diagnostic evaluation for clinical endpoints, close monitoring for toxicity, and facilities for processing, storing, and shipping of specimens for virologic, microbiologic, and immunologic testing. These first two "layers," supported by grants, would together provide the capability for initial exploratory studies and for advancing this early work to Phase IIB/III studies. Existing Phase III programs, such as SOCA, should be integrated into the core NIAID trials infrastructure. Existing Phase I/IIA programs, such as AMC, must be adequately funded to assess variables relating to the underlying HIV disease process; collaboration with the central network for the conduct of Phase IIB-IV studies must be established.

The network described above must have the flexibility to meet the scientific challenges of therapeutics research as they arise. A funding mechanism, such as a master contract, that will permit rapid expansion and contraction of the network's research units as the scientific need dictates is key. Such a mechanism would ensure access to sufficient numbers of patients with diverse demographic characteristics for Phase IV and some Phase III trials. In addition, individual clinicians who meet specific criteria should have the opportunity to participate in Phase IV trials on a protocol-by-protocol basis with capitated contractual support. These large studies, evaluating fairly well-characterized agents and requiring minimal data collection, need much less intensive clinical and toxicity monitoring. The possibility for such expansion of the accessible patient and investigator base will enable the network to successfully mount the large trials needed to define strategies for optimal standard-of-care management.

For the optimal effectiveness of this clinical trials network, strong scientific leadership must be exerted by the investigators. The system must be an open one that entertains excellent research ideas from investigators regardless of whether they are supported by network funds. This applies not only to proposals for innovative clinical trials, but also to ideas for pathogenesis and translational proof-of-concept research. A mechanism similar to a letter of intent could be established so that independent, peer-reviewed research projects could utilize the network's resources.

Collaborative research projects with other Institutes involved in HIV/AIDS clinical trials would permit optimal utilization of the network's scientific and patient resources and must be encouraged. Building on the core trials infrastructure provided by NIAID, each relevant Institute should contribute scientific

guidance within its area of expertise, as well as supplementary funding for trials and other resources (such as tissue banks and central reading centers), rather than create anew the full capability to conduct comparative Phase III and IV trials. Collaborative efforts can be expected to result in a more economical use of NIH resources as well as the best possible science.

Recommendation

V.2 A uniform standard for clinical trials databases should be developed to ensure that data can be shared between studies both within and across trials programs.

Uniform standards that apply at least to a minimal dataset of key baseline, outcome, compliance, and toxicity data would permit cross-study analyses and longitudinal followup of participants. Data-sharing capability will facilitate collaboration and cooperation among AIDS Phase I/IIA and IIB-IV clinical trials efforts. All future NIH trials should be subject to such standards.

Pediatric AIDS Clinical Trials

The pediatric ACTG (PACTG) conducts all NIH-sponsored extramural AIDS clinical trials in children. The PACTG is, at present, a conjoint effort that melded two originally separate programs funded by NIAID and NICHD. The necessity to integrate the two arose from the realization that there was a very limited patient population available for enrollment into trials. Dual sponsorship utilizing different funding mechanisms continues. The two groups are now integrated with respect to scientific leadership.

The PACTG is to be congratulated for their successful demonstration that AZT therapy of HIV-infected pregnant women and their newborns can reduce substantially the risk of perinatal transmission. However, the PACTG has been slow to initiate studies to identify even more effective interventions and to exploit opportunities to define basic pathogenic mechanisms of pediatric AIDS and analyze the effects of HIV infection on the developing immune system. This may derive from a failure of the PACTG leadership to seek out external scientific advice.

There are indications that prenatal HIV testing and the administration of effective therapy are already affecting HIV transmission rates. If perinatal transmission is successfully curtailed in the United States, the domestic pediatric clinical trials effort will require careful reexamination. A timely consideration of the optimal means to carry out clinical pediatric AIDS research in the future is essential, particularly since the pediatric AIDS problem will continue to grow worldwide. To maximize the productivity of domestic pediatric AIDS clinical trials, the NCI intramural pediatric AIDS program should be interdigitated with the PACTG. The Working Group believes that the pediatric AIDS clinical trials program would benefit from outside advice.

In addition, the Working Group believes that, while pediatric trials are understandably more expensive than those in adults, substantial savings can be achieved without disrupting this effort.

Recommendation

V.3 The Working Group recommends an early reexamination of the optimal approach to future pediatric AIDS clinical trials. Furthermore, significant reductions in allocations to the PACTG are recommended. These should be implemented in such a manner so that the essential clinical trials function of the PACTG is not impaired.

Oversight for all NIH-Sponsored AIDS Clinical Trials

To maximize the quality and productivity of all adult and pediatric clinical trial activities sponsored by the NIH, the Working Group recommends:

Recommendation

V.4 An oversight committee for all NIH-sponsored AIDS clinical trials should be created that is based in the OAR and includes broad scientific and community representation.

This oversight committee will make recommendations to the OAR Director and should be charged with developing an overall mission statement for NIH-sponsored therapeutics research and with ensuring the coordination of all NIH-sponsored HIV clinical trials efforts. It should be the responsibility of this group to provide broad scientific direction, prevent unnecessary overlap and competition, and identify the resources needed. The committee would focus primarily on inter-Institute issues. Certain activities now located within NIAID, such as the AIDS Clinical Drug Development Committee that evaluates candidate therapies for inclusion in NIAID clinical trials, might logically be assumed by this committee. The oversight committee could then outline an overall NIH drug development plan across Institutes, networks, and adult and pediatric populations. This group should develop a policy regarding the performance of studies that are redundant to industry efforts; NIH-sponsored trials programs should not study investigational or marketed agents unless these studies will test novel hypotheses and would not have otherwise been conducted by industry. NIH has funded clinical studies that could be carried out equally well by pharmaceutical companies that could profit significantly from positive outcomes. The Working Group believes that such clinical studies should be conducted and financed by the companies unless there are specific important objectives for either patient care or scientific relevance that would otherwise be delayed or not carried out. In these instances, cofunding by industry would be appropriate and should be explored.

The Working Group notes that the NIH Director recently created a committee to determine what clinical research is appropriate for NIH sponsorship. In this regard, the oversight committee should take its lead from the NIH-wide policies being developed. This committee should be constituted as soon as possible, so that it may guide the development of the proposed integrated network.

VI. DRUG DISCOVERY RESEARCH

Refocus and restructure the drug discovery research effort

NIH drug discovery efforts encompass a wide range of scientific disciplines. The Working Group and Drug Discovery Area Review Panel found marked differences in the quality of research supported by AIDS funds. Some programs, such as those focused on structural studies of HIV molecular targets and the National Cooperative Drug Discovery Groups for OIs (NCDDG-OIs) are well organized and productive. For instance, the Working Group found that the multidisciplinary approach to determining the molecular structure of HIV-proteins supported by the National Institute for General Medical Sciences (NIGMS) was exceedingly successful, resulting in the characterization of a number of potential therapeutic targets and agents. Such basic science efforts and others like it need continued support and emphasis. The NIAID NCDDG-OIs has successfully developed agents that have subsequently entered clinical trials. Other NIH drug development programs could be improved and/or better coordinated. The Drug Discovery Area Review Panel report makes detailed recommendations in specific areas.

In considering NIH's AIDS drug discovery efforts, some members of the Working Group questioned whether having a program that replicates the functions of the pharmaceutical industry is the best use of NIH resources. For example, these members felt that NIH's proper scientific function is to support the development of mechanism-based screens rather than support a screening program *per se*. Certainly, research required to develop such screening assays is clearly a high priority for NIH. There may be unique drug development situations that require more extensive Federal support, particularly research on "orphan" diseases, such as treatment of certain AIDS-associated OIs, where there is limited or no commercial interest. The availability of NIH resources to support such drug discovery research is certainly warranted.

One large endeavor, the NCI drug discovery program, located within the Developmental Therapeutics Program (DTP), requires review and restructuring. The scope of the DTP effort essentially replicates that found in the pharmaceutical industry: resources are allocated for acquisition of natural and synthetic products, screening, medicinal chemistry, synthesis, characterization of mechanism of action, pharmacology, and toxicology. Although this program identified active agents in the mid-1980s when its cell-based antiviral screen was the only assay available, DTP's continued dependence on this nonselective screen is no longer warranted. Since the screen is not aimed at specific molecular targets, compounds identified as active may have the same target as agents already well studied in the clinic, as has been the case for the non-nucleoside reverse transcriptase inhibitors identified by DTP. The few agents that have advanced to further study represent a restricted number of antiviral mechanisms, and no truly novel agent has reached the clinic. The overall program is rather diffuse, in spite of the fact that day-to-day management of its many component branches, laboratories, and contractors appears to be well integrated. As a result, the productivity of this program over the last 8 years has been limited. Although the basic research studies that have elucidated the mechanism of action of active compounds have been of good quality, these studies have not met the goal of discovering truly novel inhibitors of HIV.

The DTP program has a unique resource in its library of defined compounds and in its various acquisition contracts, particularly for natural products. The program also has substantial capabilities in medicinal chemistry, in the characterization of drug mechanisms, and in the assessment of toxicology and pharmacology sufficient to support the filing of an investigational new drug (IND) application with

the FDA. Because the pharmaceutical industry's continued active interest in drug discovery for HIV and its associated OIs and malignancies cannot be assured, maintenance of a drug discovery infrastructure supported by NIH may be justifiable. However, resources would be better utilized if the DTP's efforts were refocused on the development of novel mechanism-based screens with high throughput capacity that are derived from basic research advances. Moreover, the DTP should use its core resources to support NIH-wide antiretroviral and opportunistic disease drug discovery research efforts; it would not be cost-effective to reproduce the considerable DTP infrastructure in other ICDs.

Recommendation

VI.1 An external scientific advisory board, including a representative from OAR, should be constituted to provide guidance regarding appropriate goals for future DTP AIDS research activities. Future assessment of the DTP AIDS drug discovery program should include its ability to support the overall NIH drug discovery effort for HIV and for the anti-OI discovery efforts of other ICDs. NCI bears a particular responsibility for the development of novel treatments for AIDS-associated malignancies. To accomplish these goals, DTP management and structure require careful review, both to determine what can be eliminated from the AIDS drug discovery effort and to appropriately assign the funds allotted to AIDS-directed research. A substantial decrease in the size and funding of the DTP's current AIDS-related drug discovery effort is appropriate.

VII. RESEARCH ON OPPORTUNISTIC INFECTIONS

Augment basic science research on AIDS-associated opportunistic infections and facilitate transfer of new findings to early clinical evaluation

Opportunistic infections (OIs) caused by a diverse range of viruses, fungi, protozoa, bacteria, and mycobacteria represent the major causes of suffering and death for HIV-infected individuals. These pathogens can affect virtually all tissues and organ systems, causing severe functional compromise and, in some instances, malignant transformation. Although prophylactic regimens have been defined that decrease substantially the risk of developing certain OIs, none of these are completely successful and all are complicated by untoward side effects, resistance development, interactions with other critical medications, or significant inconvenience. Effective therapeutic strategies have been developed to treat specific OIs once serious infection takes hold. However, none of these therapies are curative and they are often toxic. Life-long suppressive therapy is typically required following recovery from the acute disease presentation.

Cumulatively, these prophylactic and therapeutic advances have made significant contributions to prolonging the lives of people with AIDS. Yet there remains a great need to develop more effective and less toxic drugs to treat OIs for which therapies are now available, and to develop effective treatments for a number of OIs where none currently exist. Much of the progress made to date in preventing and treating AIDS-associated OIs has come from the improved use of drugs that had been developed previously to treat other infections, although a limited number of new drugs has been developed specifically for use in HIV disease. Advances in the treatment and prevention of AIDS-associated OIs has also benefitted other immunocompromised patients.

Few new drugs have been developed specifically to treat OIs in people with AIDS. There appears to be limited interest on the part of pharmaceutical companies to support significant drug development efforts for a number of OIs that are unique to or are most commonly seen as complications of AIDS.

NIH-sponsored researchers generate much of the basic science information about the biology of the pathogens responsible for AIDS-associated OIs. Such advances in our understanding of these pathogens will be needed for any successful drug development effort. However, it is exceedingly difficult to advance basic laboratory findings to the stages of drug development, manufacture, and initial clinical evaluation. Should this situation continue, the Working Group is concerned that the pace of development of new, more effective and less toxic therapies to prevent and treat AIDS-associated OIs will be far too slow. Future progress in preventing and treating AIDS-associated OIs will depend on progress in understanding the fundamental biology and pathogenesis of these diseases. To best accomplish this goal, investigators with expertise in microbiology, cell biology, genetics and cancer biology should be encouraged to contribute to the study of AIDS-associated OIs. As with all other areas of AIDS research, there is a great need to attract and support young investigators in these areas.

Recommendations

VII.1 Reinvigorate the basic science research effort on AIDS-associated opportunistic infections, emphasizing studies of fundamental aspects of the biology of the responsible microorganisms and the mechanisms of disease pathogenesis.

VII.2 The NIH should pursue innovative approaches, such as enhancing the quality and AIDS focus of the Small Business Innovative Research (SBIR) grant program, to foster the transfer of new laboratory findings to early "proof of concept" clinical evaluation.

The NIH currently supports a program of basic and applied research on OIs, and the Working Group recommends an increase in the effort. It is expected that the productivity of this effort will be enhanced significantly by the recommendations discussed elsewhere in this report, including: increased support for investigator-initiated research efforts; efforts to inform peer review groups of the scientific priorities of the NIH Plan for HIV-Related Research; increased efforts to encourage new and junior investigators to enter AIDS research; and increased efforts to attract established investigators with expertise in related areas to pursue AIDS-related research.

To enhance progress in this area, the OAR and relevant ICDs should increase and better coordinate their efforts to foster research on AIDS-related OIs and continue to solicit the advice of non-Government scientists in identifying new research needs and opportunities. As many of the AIDS-associated OIs also cause disease in individuals with other types of immunodeficiency, and research on these pathogens is consequently supported with both AIDS and non-AIDS funds, it will be important to view the NIH portfolio in this area as defined by scientific topic rather than funding mechanism.

VIII. COMPLEMENTARY AND ALTERNATIVE MEDICINE RESEARCH

Strengthen the scientific base for the assessment of complementary and alternative medicine (CAM) therapies for HIV disease

In the course of the evaluation process, the issue of the appropriate role of the NIH in facilitating the evaluation of CAM therapies for HIV infection and its complications was considered. There are a number of reasons why attention to this issue is important: CAM therapies are widely utilized by people with HIV; they may have potential benefit; they may have potential harm; and the perceptions of their efficacy may enhance or interfere with an individual's use of "conventional" therapies for HIV disease.

Although the reasons are clear, a number of obstacles have confronted individuals who have wanted to test the efficacy of specific CAM therapies. These obstacles have limited progress in evaluating the potential benefits or dangers of CAM therapies in widespread use. Advocates of CAM therapies for HIV disease have argued that the NIH should institute a significant new research initiative in this area, supported by substantial funding. Detractors have made the case that it is simply not possible to test all agents presently being used by persons with AIDS. To investigate these issues, the Working Group established a subpanel of researchers and advocates interested in these issues and solicited input from interested proponents of CAM therapies. Based on input received from these sources, the Working Group believes that additional attention to this topic is needed.

It is the view of the Working Group that the most meaningful and effective action for the NIH to take to advance the study of the potential benefits or harms of CAM use for HIV disease will be to strengthen the scientific basis for future CAM research in HIV disease. An OAR effort toward this end should be undertaken in close collaboration with the NIH Office of Alternative Medicine (OAM), where significant expertise already exists concerning CAM research needs and challenges. The Working Group therefore recommends that the following activities be pursued:

Recommendations

VIII.1 The OAR should establish an *ad hoc* advisory group to communicate community interest in the area of CAM therapies for HIV disease and to help identify therapies with apparent promise or potential danger for persons with HIV infection. This advisory group should consist of scientists experienced in clinical and laboratory evaluation of candidate therapies for HIV infection or its complications, and community representatives, including individuals who use CAM therapies.

VIII.2 A catalog should be prepared of all research relating to HIV-related CAM therapies currently being supported by the NIH. OAR and its *ad hoc* advisory group should work with the OAM to establish an operational definition of CAM therapy as it relates to HIV disease and to construct a taxonomy to categorize CAM therapies in this area.

VIII.3 The OAR and its ad hoc advisory group should work with the OAM to sponsor a workshop on the research methodology for the evaluation of the efficacy of CAM therapies for HIV disease. The OAR also should work with the OAM to sponsor workshops to educate individuals interested in the evaluation of candidate CAM therapies for HIV disease about

the preparation of NIH grant applications and the processes by which such applications are evaluated.

VIII.4 The OAR should work with the OAM and DRG to suggest individuals to serve as *ad hoc* members of IRGs that are reviewing HIV CAM therapy research proposals. Criteria for the selection of such members should include those currently utilized by DRG to select IRG members, as well as experience in the scientific evaluation of novel therapeutic approaches and knowledge of the concepts and practices of CAM therapies.

IX. REGIONAL PRIMATE RESEARCH CENTERS

Reorganize procedures to ensure that Centers are available and responsive to non-Center-affiliated scientists

The National Center for Research Resources (NCRR) Regional Primate Research Centers (RPRCs) are a critically important resource for the scientific community. Nonhuman primates and the SIV/SHIV models of infection are critical to testing drugs and vaccines, investigating the mechanisms of infection and pathogenesis, and evaluating novel concepts for interfering with virus infection and consequent disease progression. The use of these model systems is an expensive but necessary part of many current research projects. The importance of these systems will almost certainly continue to grow in the future. To ensure the maximal productivity of research involving nonhuman primates, it is essential that the most able scientists be supported to conduct high-priority studies. However, it is the Working Group's view that the current funding structure for research using primate models does not necessarily support the most meritorious research. Currently, NIH AIDS support is distributed to the RPRCs where it is used to support projects initiated and carried out by investigators at the RPRC. There are many excellent investigators at the RPRCs. Nonetheless, RPRC funds are not available for the support of non-RPRC researchers who may have equally, if not more, deserving research proposals. The inherent expense of research involving nonhuman primates makes it difficult to obtain adequate support for projects involving these animals through the R01 funding mechanism. Thus, the present NIH funding structure for primate research does not permit all investigators with meritorious ideas equal access to this scarce resource. To address these concerns, the Working Group recommends:

Recommendation

IX.1 The OAR should commission a panel to define optimal mechanisms to support AIDS research at the RPRCs and to devise strategies that permit the most promising research ideas to be tested.

The goal of the panel will be to define mechanisms for the support of research involving nonhuman primate models so as to provide equal access to all members of the AIDS research community while maintaining the quality and vigor of the RPRC programs. The panel also should provide advice on operational aspects and infrastructure needs.

It is essential to maintain the quality of the infrastructure and animal care activities carried out by the RPRC staffs. Even if funding to the RPRCs must be increased to attain those goals, the Working Group feels that the benefit in the quality of research obtained by these changes is worthwhile. The Working Group recommends that the following approach be considered by this panel for implementation in the near future:

Recommendation

IX.2 The process for competition of NCRR AIDS supplemental funding should be opened up to all extramural investigators.

Investigators interested in conducting experiments involving animals would apply to the individual RPRCs for support derived from NCRR AIDS supplements. These proposals would be reviewed by an

external advisory committee at each RPRC. Those projects deemed most worthy would be supported. At the time of renewal of the RPRC grant, the review should place heavy emphasis on the RPRC's success in attracting and supporting quality research studies. The panel recommended above should investigate the possibility of providing seed funds to bring new, non-RPRC investigators into RPRC-supported studies in the future.

Recommendations

IX.3 To optimize the quality and productivity of AIDS research conducted at the RPRCs, the NCRR IRGs that review the Centers should be strengthened by the addition of scientists with expertise in AIDS and AIDS-related research.

IX.4 Open competition for funds to support relevant animal costs included in DRG-reviewed grants might be accomplished through a regularly recurring RFA.

X. AIDS RESEARCH CENTERS

Strengthen AIDS Research Centers to promote multidisciplinary research on the disease

The challenges posed by AIDS require both biomedical and behavioral interventions; AIDS is a multisystem and multiorgan disease, involving malignancies, OIs, and neurological, gynecological, ocular, oral, dermatological, and gastrointestinal complications, affecting people across the life span from infancy to old age. AIDS Research Centers can provide a central pool of resources capable of a flexible and coordinated response to new scientific opportunities. There are many advantages to bringing together basic, clinical, epidemiological and behavioral scientists in research centers. A central pool of resources provides the Center with flexibility and allows a rapid and coordinated response to new scientific opportunities. Translating basic laboratory and behavioral sciences research into public health and clinical practice is an essential aspect of a Center's program that can, in turn, provide further basic research opportunities. Centers also are ideal locations for interdisciplinary training, which can build upon the academic and clinical strengths of an institution. In addition, Centers have a greater capacity to leverage institutional donor and community support.

Currently, 16 AIDS Research Centers are funded by NIH. Twelve of these are supported by the Centers for AIDS Research (CFARs) mechanism and four are supported through the comprehensive research center mechanism. Of the CFARs, 11 are funded by NIAID and 1 by NIMH. All 4 comprehensive AIDS research centers are funded by NIMH. The CFAR programs were recently reviewed and recompeted. Weaker CFAR programs have been eliminated; current CFARs are viewed as generally productive but considerably hampered by a recent reduction in total funding per Center. The Working Group considered the current levels of CFAR support to be, in many instances, too low to build and maintain adequate infrastructure and core support.

The CFARs should have strong core facilities to support Center-funded initiatives and investigator-initiated research grants. They also should have strong community ties. The level of support for infrastructure and core facilities of individual Centers should be determined by a formula and be in proportion to the Center’s ability to obtain R01 grants. Centers should maintain flexibility to bring together interdisciplinary research. Incentives should be provided to encourage epidemiological and behavioral research components at the centers.

The success of an AIDS Center is dependent upon the caliber of its leadership, the quality of its science, the integration of its programs, the ability to foster collaborations, and the strength of its training and mentoring of scientists around a common research theme. The leadership abilities of the Center director should be one of the key criteria in determining Center support.

Recommendations

X.1 The Working Group recommends that funding for the CFAR program as a whole be increased by approximately 50 percent. This would allow annual funding in the range of $750,000 to $1.5 million per year, to be allocated in proportion to a Center’s research capacity and its ability to build an interdisciplinary research program and attract R01s.

X.2 The comprehensive research centers program, funded by NIMH, has been found to be productive and should be maintained.

XI. REPOSITORIES AND DATABASES

Ensure that central repositories of biomedical specimens and databases are of the highest quality and accessible to qualified investigators

NIH research on HIV prevention, transmission, natural history, and treatment has generated sizeable repositories of biomedical specimens and large databases of information. Although these repositories and databases are potential national research treasures, they currently are poorly coordinated, and many investigators have little or no access to them. To be optimally used, repositories and databases must be linked to an informative and readily accessible tracking system that is widely available to the scientific community. Procedures for accessing samples and data must be clearly delineated, fair, and peer-reviewed. Indeed, the Working Group notes that some research networks are making progress in the development of procedures for accessing specimens. Future development of repositories and databases should be investigator-driven and prospectively planned, based on cogent research hypotheses. Ideally, planning for repositories should involve scientists knowledgeable in virology, immunology, and pathogenesis research and should involve collaborations with clinicians and epidemiologists. This would insure that appropriate specimens and data are collected and increase the likelihood that they will be used. NIH should pursue linkages to privately-held specimen repositories, such as those containing samples from industry-sponsored clinical trials.

Recommendation

XI.1 Improvements should be made in repositories and databases in accord with three principles: repositories and databases should be investigator-designed and hypothesis-driven; accessible to all qualified investigators; and coordinated under a new user-friendly central tracking system maintained under the auspices of the OAR. Support should be provided for collection of specimens, as dictated by scientific needs, and for these repositories and databases.

XII. AIDS RESEARCH INFORMATION SYSTEM

Upgrade the NIH AIDS Research Information System and increase the information base

Throughout the course of the review, the Working Group, the six panels, and the component subpanels utilized a number of NIH database systems, including the OAR AIDS Research Information System (ARIS), to secure AIDS-related grant and contract information and to gain a better understanding of the NIH AIDS portfolio. The Working Group recognizes that, while ARIS represents a unique NIH database, it must be improved. ARIS must contain all budget and relevant program information on every grant and contract coded as AIDS and AIDS-related.

The Working Group concluded that the NIH information databases were inadequate to provide information for this review. The work of this evaluation was significantly hampered by both the difficulty in obtaining information and the quality of the information available from the databases. For many large programs listed in ARIS, the only retrievable information provided to the system by the ICDs was project number and funding level. Some projects were identified by the ICDs only as "AIDS Research" or "Cancer Center," and thus elusive to any analysis.

The Working Group concluded that the lack of a complete, accurate, and reliable information database is simply an unacceptable situation that hampers the OAR Director and the NIH Director from being able to fulfill their responsibilities in directing, managing, and accounting for the AIDS-research portfolio. The Working Group and the panels acknowledge and appreciate the considerable time and effort from Institute and Center Directors and their staffs who worked very hard to provide information for this review, filling the gaps from an inadequate database system. However, the Working Group believes it is time for the OAR and NIH to develop a more advanced and comprehensive information system to track the entire NIH AIDS research portfolio, including both intramural and extramural awards. The Working Group also realizes that an information system will be useful only if all relevant information is provided to it by the ICDs.

Recommendation

XII.1 A new information database system should be developed containing grant, contract, or intramural project titles and numbers; names of principal investigator and institutional affiliations; budget amounts; funding ICDs; and an abstract for each proposal. In addition, the Working Group recommends that a yearly summary abstract of ongoing activities and list of publications resulting from each award be prepared by the principal investigator and included in the database. The database should contain this information for every project coded by the ICDs as AIDS or AIDS-related.

Information in the database should be regularly updated. This information must be easily and readily retrievable by searching for any of the parameters listed above and by research topic area. The ICD should assign an OAR Strategic Planning code for each grant, contract, or intramural project included in the database. The OAR should periodically monitor and review the assigned strategic plan codes to ensure that they adequately characterize the research conducted.

The Working Group's examination of information available from other existing NIH databases revealed similar problems. OAR should develop a system to manage NIH AIDS research project information that

could serve as a model for NIH non-AIDS information databases. It is essential that the AIDS and non-AIDS information databases be compatible and have an identical information format so that they provide an efficient means to obtain information critical in planning, budgeting, managing, and evaluating NIH research programs.

XIII. DEFINITIONS OF AIDS AND AIDS-RELATED RESEARCH

Develop and implement a clear definition of AIDS and AIDS-related research through an evolving process

In the review of the current NIH AIDS research programs, the Working Group and Area Review Panels found that many ICDs have not developed an operational definition of AIDS and AIDS-related research for the purposes of assigning AIDS-designated funds. This has been a major issue encountered during the course of the review.

The coding of projects as AIDS, AIDS-related, or non-AIDS currently is the responsibility of each ICD; thus, coding can vary according to the different missions of the ICDs. Examples are noted throughout the individual panel reports of projects that are inappropriately classified as AIDS or AIDS-related. In some ICDs, most notably NCI, inappropriate classification has led to allocation of AIDS research funds to activities with little or no direct relevance to AIDS. Similarly, programs sponsored by the National Heart, Lung, and Blood Institute (NHLBI) for the development of artificial blood substitutes have been supported with AIDS research funds. Although such research may be highly meritorious, supporting it with AIDS resources is inappropriate, since previous successful research has provided the means to protect the blood supply from HIV.

The NCI, through leadership of its new Director, is currently developing, in cooperation with the OAR, a coding system for AIDS and AIDS-related projects that should result in a more accurate and reliable system for classification of all NCI intramural and extramural programs and projects. Furthermore, the NCI Director has recently announced the redirection of $30 million from intramural research to fund new extramural research. This redirection of resources will permit expansion of the NCI AIDS Malignancy Consortium. It will also allow funding of many investigator-initiated AIDS research grants that had fallen below the payline in other ICDs. The Working Group acknowledges NCI's example as a model of how an ICD can begin to redress its historical problems of inappropriately classifying research as AIDS-related.

Recommendations

XIII.1 The Working Group has determined that a substantial proportion of NIH AIDS funds has been previously and is presently inappropriately classified as AIDS or AIDS-related by many ICDs. Such funds should be redirected to research programs appropriately classified as AIDS and AIDS-related. It is recognized that an orderly plan for redirection is needed and that its implementation may require a period of time.

XIII.2 The Working Group strongly recommends that the OAR, in cooperation with the ICDs, develop guidelines/criteria for the classification and coding of projects as AIDS and AIDS-related. Such a coding system should be implemented immediately to permit multiyear analyses of projects by these categories. The Working Group recognizes that these guidelines may evolve as AIDS research priorities change. It is crucial that this coding system be developed to ensure that AIDS research funds are effectively, efficiently, and optimally utilized.

The OAR and the ICDs should jointly develop definitions of AIDS and HIV-related research. These definitions should evolve with time and should not be viewed as immutable. OAR should include definitions of AIDS and AIDS-related research in the annual NIH Plan for HIV-Related Research and should be responsible for ensuring that the definitions are consistent among the various ICDs.

A second major issue in project coding relates to support for basic research. Studies in the fields of molecular biology, structural biology, immunology, and virology have provided the scientific foundation for rapid advances in AIDS research. Support for basic research is crucial, as this research has the potential to advance research on many diseases. However, the question remains: How much basic biomedical and behavioral research should be supported with AIDS research funds?

Recommendation

XIII.3 AIDS funds should continue to support excellent work in selected underdeveloped areas of basic research judged to be likely to make substantial contributions to progress against this disease and its sequelae. The research areas for potential investment should be clearly identified in the annual NIH Plan for HIV-Related Research so that they can be targeted for NIH-wide additional support.

XIV. OFFICE OF AIDS RESEARCH

Preserve a strong OAR to provide leadership and coordination to the entire NIH AIDS research program

The Working Group and panels unanimously agreed that there is a crucial need for a continued strong and viable OAR to provide overall scientific leadership and coordination of NIH AIDS research. This endeavor requires vision and direction that spans the scientific disciplines and Institute missions.

The OAR budget authority for all intramural and extramural AIDS research, mandated by the NIH Revitalization Act of 1993, must be preserved. Anticipated budgetary constraints over the next 5 years will place even greater demand on the limited funding available for AIDS research, thus making OAR's management and priority-setting roles even more significant. OAR's authority to develop and implement the annual AIDS research plan and budget is essential. OAR should increase its efforts to coordinate AIDS research activities among the ICDs and with other agencies in order to improve information exchange and eliminate duplication of efforts. OAR's collaborative activities should also extend to private foundations, pharmaceutical and biotechnology companies, and international agencies.

The Working Group acknowledges the continued support of the NIH Director for the functions and authority of the OAR. The Working Group emphasizes that the NIH Director's visible support is crucial for the implementation of the recommendations of this report.

Recommendation

XIV.1 The OAR should immediately develop a plan to implement the recommendations in this evaluation report.

The Working Group recognizes this report and the accompanying Area Review Panel reports contain an extensive series of specific recommendations. We also recognize that major initiatives and programs often require up to 18 months to progress from a developmental stage to the actual awarding of grants and contracts. Therefore, it is imperative that an implementation plan be developed immediately so that these recommendations can be incorporated in the FY 1997 and FY 1998 NIH AIDS research budget and planning processes.

Bias and Conflict of Interest Statement

The Evaluation Working Group and the six Area Review Panels were charged with reviewing, evaluating, and developing recommendations for the future of the NIH AIDS research program. The program currently has a budget of approximately $1.4 billion and involves initiatives supported by virtually all ICDs. The NIH AIDS research portfolio spans basic, clinical, epidemiologic, and behavioral research, as well as vaccine and drug development. It is funded through a range of mechanisms and is conducted by a diverse community of researchers representing a broad range of scientific disciplines.

In order to evaluate the NIH AIDS research program thoroughly and to provide appropriate and useful recommendations for its future direction, it was necessary to involve individuals with both scientific expertise and familiarity with the NIH system. This included researchers, clinicians, activists, and service providers diverse in scientific discipline, institutional affiliation, geographic base, race/ethnicity, gender, and HIV serostatus (which was voluntarily self-revealed by some). The 114 people involved in the review process came from Government, universities, private research institutions, community organizations, and pharmaceutical and biotechnology companies.

It was recognized that with the appropriate expertise and familiarity comes the likelihood that there is potential for bias and conflict of interest—both perceived and real. In an effort to minimize such bias and conflict, a number of steps were taken (similar to the process used by the National Academy of Sciences and its affiliates). First, input was solicited from a wide range of researchers as well as representatives of the infected and affected community for nominees to serve on the Area Review Panels. The selection of Panel members from resulting lists was based on expertise (both AIDS and non-AIDS) and familiarity with HIV/AIDS issues, and was made by each Area Review Panel Chair in consultation with the Working Group Chair. Every effort was made to balance the Panels with individuals who represented different points of view and had different levels of linkage to the NIH AIDS research program.

Second, at the initial meeting of the Working Group and the Area Review Panels, members were asked to declare their own potential biases and conflicts and to discuss these as a group. Third, individuals recused themselves from participating in activities that posed an obvious conflict (e.g., serving on subpanels that reviewed programs that included their own grants). Fourth, any reviews conducted by individuals or subpanels that could be perceived to have a conflict were subject to secondary review by others with no potential conflict. Finally, the reports generated by the individual Panels and the Working Group were subject to lengthy discussion and debate and were not finalized until consensus was reached.

Appendix A

BIOGRAPHICAL SKETCHES

NIH AIDS RESEARCH PROGRAM EVALUATION WORKING GROUP

Arnold J. Levine, Ph.D., *Chair,* is the Chairman and Harry C. Weiss Professor of the Department of Molecular Biology at Princeton University, and a member of the National Academy of Sciences and the Institute of Medicine. He received his Ph.D. from the University of Pennsylvania and completed his postdoctoral training at the California Institute of Technology. He is an eminent researcher in virology-oncology, and author of over 277 scientific publications, and the recipient of numerous awards, including the Bristol-Myers Squibb Award for Distinguished Achievement in Cancer Research, the Ciba Drew Award in Biomedical Research, the Shubitz Award from the University of Chicago Cancer Research Center, the Thomas A. Edison Science Award, and the first annual Strang Award from New York Hospital/Cornell Medical Center. In 1994, he was awarded the Docteur Honoris Causa, University Pierre and Marie Curie, Paris.

Harold S. Ginsberg, M.D., *Co-Chair*, is an Expert Scientist at NIAID and the Eugene Higgins Professor of Medicine and Microbiology, Emeritus, College of Physicians and Surgeons at Columbia University. He is a member of the National Academy of Sciences and the Institute of Medicine. He serves on the Board of Governors of the American Academy of Microbiology and the U.S. National Committee for the International Union of Microbiological Societies. He co-chaired the Institute of Medicine Roundtable for the Development of Drugs and Vaccines Against AIDS and has chaired the NIH Ad Hoc AIDS Study Section. He also has been a Vice President, International Committee for Nomenclature of Viruses of the International Association of Microbiological Societies. Dr. Ginsberg has received numerous awards, including the Senior U.S. Scientist, Humboldt Award; the Physicians and Surgeons Distinguished Service Award; and the Bristol-Myers Squibb Award for Distinguished Achievement in Infectious Disease Research. He is an Honorary Fellow of the American Association for the Advancement of Science and was a Fogarty International Scholar in 1992. After graduating from the Tulane University School of Medicine, Dr. Ginsberg served in World War II, achieving the rank of Lieutenant Colonel and was awarded the Legion of Merit.

Barry R. Bloom, Ph.D., is an Investigator at the Howard Hughes Medical Institute and the Weinstock Professor of Microbiology and Immunology at the Albert Einstein College of Medicine in New York. He received his B.A. degree and an honorary Sc.D. from Amherst College, and his Ph.D. from the Rockefeller University. Dr. Bloom chaired the Tuberculosis Committee at WHO and is currently the Chair of the Scientific and Technical Advisory Committee to the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. Dr. Bloom served as a consultant to the White House on International Health Policy during 1977-78. He has served as a member of the National Advisory Council of NIAID, its AIDS subcommittee, and the U.S. National Vaccine Advisory Committee. He is currently Co-Chair of the Board on International Health of the National Research Council of the National Academy of Sciences. He serves as a member of the WHO Ad Hoc Committee for Research Priorities and on the NAS Committee on Criteria for Federal Support of Federal Research and Development. In 1991, he received the first Bristol-Myers Squibb Award for Distinguished Research in Infectious Diseases. Dr. Bloom also is a member of the National Academy of Sciences, a

member and Councillor of the Institute of Medicine, and a member of the American Academy of Arts and Sciences.

Rebecca H. Buckley, M.D., is the J. Buren Sidbury Professor of Pediatrics and the Chief of the Division of Pediatric Allergy and Immunology at the Duke University Medical Center. She is an internationally known researcher with a bibliography of over 200 scientific publications in the field of immunology, specifically in the areas of normal and abnormal development of the immune system, primary immunodeficiency diseases, and acquired immunodeficiency. Dr. Buckley is a member of the American Association of Immunologists. She currently is the Associate Editor of the *Journal of Clinical Immunology*. From 1984-87, she chaired its Clinical Immunology and Immunopathology awards committees. Dr. Buckley has served on numerous advisory councils and committees, including the Medical Advisory Committee of the Immune Deficiency Foundation, the Scientific Advisory Committee of the Allergy and Immunology Institute of the International Life Sciences Institute, and the Board of Scientific Counselors to the NIAID, NIH.

Charles C.J. Carpenter, M.D., is Professor of Medicine and Director of the International Health Institute at Brown University; the President of the Johns Hopkins Medical and Surgery Association; Chairman of the Section on Medical Sciences, American Association for the Advancement of Science; Chairman of the Office of AIDS Research Advisory Committee (OARAC); and Chairman of the NIH Data Safety Monitoring Board for AIDS Clinical Trials Group. He is a member of the Institute of Medicine and served on its Committee on Research Grants and its Board of Science and Technology for International Development and has chaired the Board of Governors for the American Board of Internal Medicine. Dr. Carpenter has served on numerous NIH councils and committees. He has chaired the AIDS Program Advisory Committee and the State-of-the-Art Conference on AZT Therapy for Early HIV Infection, and has served as a member of the NIAID Council and the Ad Hoc Consultants to the NIH AIDS Executive Committee. For 20 years he also served as a member of the WHO Expert Advisory Committee on Bacterial Diseases, and he currently chairs the U.S. Delegation to the U.S.-Japan Cooperative Medical Science Program.

Don C. Des Jarlais, Ph.D., is the Director of Research of the Chemical Dependency Institute at Beth Israel Medical Center, Professor of Epidemiology and Social Medicine at Albert Einstein College of Medicine, and a Senior Research Fellow at the National Development and Research Institute. He served as the New York State Coordinator for AIDS Research and the Assistant Deputy Director for AIDS Research Evaluation. As a leader in the fields of AIDS research and intravenous drug use, his bibliography includes over 200 publications, and he has made 1,000 presentations on AIDS and AIDS-related topics that include the plenary addresses at the third and fourth International Conferences on AIDS. He serves on numerous advisory committees for the CDC, NIDA, the National Commission on AIDS, and the National Academy of Sciences. He is Vice Chair of the Committee of AIDS Research and the Behavioral, Social, and Statistical Sciences that was established by the National Research Council of the National Academy of Sciences.

Anke A. Ehrhardt, Ph.D., is the Principal Investigator and Director of the HIV Center for Clinical and Behavioral Studies at the New York State Psychiatric Institute and College of Physicians and Surgeons at Columbia University. The Center was established in 1987 with a 5-year award by the NIMH and NIDA, and received renewal in 1993 for a second 5-year term. Dr. Ehrhardt is a Research Chief at the New York State Psychiatric Institute and a Professor of Medical Psychology in the Department of Psychiatry at Columbia University. She is an internationally known researcher in the field of sexual and

gender development of children, adolescents, and adults who has, over 25 years, amassed a bibliography with 140 scientific publications. From 1962 to 1964, as a member of the Department of Pediatrics at the University Medical School of Hamburg, West Germany, she assessed and treated children and adolescents who were victims of incest. In 1964, she joined the Psychohormonal Research Unit at Johns Hopkins University Hospital, under the direction of Dr. John Money. Dr. Ehrhardt, and Dr. Money co-authored the book *Man and Woman, Boy and Girl* in 1972. Since 1987, Dr. Ehrhardt's research has included a wide range of studies on determinants of sexual risk behavior among children, adolescents, heterosexual women and men, and the gay population, and on comprehensive approaches to prevention of HIV and STD infection. She received an award by the State of New York for "Excellence in Research" in 1990 and received the Distinguished Research Leadership Award given by the American Psychological Association in 1996.

Mark Harrington, a writer and AIDS activist, is a member of the Board of Directors, Treatment Action Group (TAG); the Community Program Advisory Committee of American Foundation for AIDS Research (AmFAR); and the Office of AIDS Research Advisory Council for NIH (OARAC). A graduate of Harvard University, Mr. Harrington has written extensively about clinical trials, therapies, opportunistic infections, and related AIDS research issues in the *New England Journal of Medicine, Morbidity and Mortality Weekly Report, Journal of the American Statistical Association, Journal of Acquired Immune Deficiency Syndromes*, as well as contributed to publications produced by ACT UP and TAG. He has served as a consultant to the FDA Antiviral Drugs Advisory Committee and the AmFAR/CRI/CCC Conference on "Organizing Community Based Clinical Trials: Models for the AIDS Epidemic." He also has served on the NIH AIDS Clinical Trials Group core committees for primary infections and opportunistic infections, the NIH/FDA GP160 advisory panel, and the Public Health Service task forces on prophylaxis and therapy for *Mycobacterium avium* complex and on anti-*Pneumocystis* prophylaxis for patients with HIV infection.

David D. Ho, M.D., is the Scientific Director and Chief Executive Officer of the Aaron Diamond AIDS Research Center for the City of New York and Director of the Center for AIDS Research at the New York University School of Medicine. He has held appointments as an Associate Professor of Medicine at the UCLA School of Medicine and as a Physician and Research Scientist at the Cedars-Sinai Medical Center and at the Harvard Medical School. Dr. Ho has published over 117 scientific publications and serves on the editorial boards of *Cellular Immunology, Journal of Virology, Journal of Experimental Medicine*, and *AIDS Research and Human Retroviruses.* He is a member of the Scientific Advisory Committees at Harvard University, Columbia University, and the University of Colorado. He was a member of the President's National Task Force on AIDS Drug Development and co-chaired its Drug Discovery subcommittee. Dr. Ho has received numerous awards and honors, including the Scientific Award of the Chinese American Medical Society, the New York Award for Excellence in Science and Technology, the Ernst June Prize in Medicine, and the Legacy Award from the Chinatown History Museum of New York. In 1994, he was elected as a Fellow of the American Association for the Advancement of Science

King Holmes, M.D., Ph.D., Natural History, Epidemiology, and Biomedical Prevention Area Review Panel Chair, is the Director of the Center for AIDS and STDs and Professor of Medicine, Epidemiology, and Microbiology at the University of Washington, Seattle. Dr. Holmes received his M.D. from Cornell University Medical College in 1963 and his Ph.D. in Microbiology from the University of Hawaii in 1967. He completed an internship in Internal Medicine at Vanderbilt University and a residency in Medicine at the University of Washington, and is board certified in Internal Medicine, with a

subspecialty in Infectious Diseases. Dr. Holmes served as Head of the Division of Infectious Diseases at the USPHS Hospital, Seattle, from 1970-1981, after which he joined the CDC as Assistant to the Director of the Division of Sexually Transmitted Diseases. From 1989-1990, Dr. Holmes was based at the Epidemiology Support and Research Unit, Global Program on AIDS, World Health Foundation, Geneva. He is a member of the Institute of Medicine.

Kiyoshi Kuromiya has been the editor and publisher of a treatment newsletter, *Critical Path AIDS Project*, since 1989. He operates a number of cutting-edge electronic services in Philadelphia, including a 24-hour AIDS treatment hotline and computer BBS, a free Internet gateway, and a comprehensive World Wide Web homepage on AIDS. Mr. Kuromiya is a founding member of ACT UP/Philadelphia and has been prominently active in civil rights, gay liberation, antiwar, and human rights movements for 35 years. As a community constituency representative of both the AIDS Clinical Trial Group and the Terry Beirn Community Programs for Clinical Research on AIDS networks, he has long been an advocate for access to treatments and treatment information (including both conventional and complementary regimens) for underserved communities including Asian-Pacific Islanders and other persons of color, incarcerated persons, and women. He serves on the faculty of the AIDS Education Training Centers, the National Advisory Board of the National Minority AIDS Council, and the advisory board for the Health Cost and Services Utilization Study (HCSUS), a project of Rand Corporation and the Agency for Health Care Policy and Research. Mr. Kuromiya also has been active in Ryan White CARE Act programs on the local, State, and national levels.

Malcolm A. Martin, M.D., is Chief of the NIAID Laboratory of Molecular Microbiology. During the past 20 years, Dr. Martin has focused his research efforts on retroviruses and concentrated on HIV. His accomplishments include the construction and dissemination of one of the most widely used full-length molecular clones of HIV-1 (NL4-3), in which all of the viral genes are intact and functional. In 1985, his group was the first to demonstrate that different HIV-1 isolates are genetically distinct and, during the past decade, he has published seminal papers describing the genetic analysis of HIV-1. More recently, he has focused on HIV-1 vaccine and disease models in subhuman primates. Dr. Martin has served on numerous NIH, USPHS, and WHO committees concerned with AIDS, the safety of retroviral vectors, and the potential hazards attending the administration of biologics. He has been honored with the NIH Director's Award, the PHS Superior Service Award, the DHHS Distinguished Service Award and, in 1990, a Presidential Executive Rank Award. He is a member of the Scientific Review Boards of the Howard Hughes Medical Institute, the Lucille P. Markey Charitable Trust, and the Aaron Diamond Foundation.

Robert Turner Schooley, M.D., is the Chair of the AIDS Clinical Trials Group Executive Committee and Director of the Colorado AIDS Clinical Trials Unit. He also is Professor of Medicine and Head of the Infectious Disease Division at the University of Colorado Health Sciences Centers. He previously was an Associate Professor of Medicine at Harvard Medical School and Acting Director of the Harvard AIDS Clinical Trials Unit at Massachusetts General Hospital. Dr. Schooley received his M.D. from Johns Hopkins University and performed research at NIH, where he became the Chief Clinical Associate of the NIAID Laboratory of Clinical Investigation. His research has focused on retrovirology and immunodeficiency viruses, and he has authored a bibliography of over 146 scientific publications. Dr. Schooley has served as a consultant and Chair of NIH study sections for retrovirology and was a member of the DHHS Task Force on AIDS Drug Development.

Phillip A. Sharp, Ph.D., is the Director of the Center for Cancer Research and the Salvador E. Luria Professor and Chair of the Department of Biology at the Massachusetts Institute of Technology. Dr. Sharp's research interests have centered on the molecular biology of tumor viruses and the mechanisms of RNA splicing. His work provided one of the first indications of the startling phenomenon of "split genes" in the cells of mammals that is crucial for understanding the genetic causes of cancer. For this work, Dr. Sharp shared the 1993 Nobel Prize in Physiology or Medicine with Dr. Richard Roberts. His other awards include the General Motors Research Foundation's Alfred P. Sloan, Jr., Prize for Cancer Research; the Louisa Gross Horwitz Prize; the Albert Lasker Basic Medical Research Award; the Gairdner Foundation International Award of Canada; and the MIT Faculty Achievement Award. In 1991, his alma mater, Union College, awarded him an honorary degree of Doctor of Human Letters. Dr. Sharp has a distinguished record of public service, which includes having served as a member of the President's Advisory Council on Science and Technology. He cochaired the committee that produced the Director of NIH's Strategic Plan and served on the Committee on Science, Engineering, and Public Policy (COSEPOP), and the Search Committees for the Directors of the National Center for Human Genome Research and the Office of AIDS Research. In the course of his 20-year scientific/academic career, Dr. Sharp has been a devoted educator/mentor and has trained more than 60 postgraduate and graduate students.

P. Roy Vagelos, M.D., is the former Chief Executive Officer of Merck & Company, Inc., where he served in this position for 9 years and was Chairman from 1986 to 1994. Earlier, he served as Chairman of the Department of Biological Chemistry and Director of the Division of Biology and Biomedical Sciences at Washington University in St. Louis. After completing his residency at Massachusetts General Hospital, Dr. Vagelos was a Senior Surgeon and then the Section Head of the Comparative Biochemistry Branch at the National Heart, Lung, and Blood Institute. The author of more than 100 scientific papers, Dr. Vagelos received the Enzyme Chemistry Award of the American Chemical Society in 1967. He is a member of the National Academy of Sciences, the American Academy of Arts and Sciences, and the American Philosophical Society. He has received honorary Doctor of Science degrees from Washington University, Brown University, the University of Medicine and Dentistry of New Jersey, New York University, Columbia University, and the New Jersey Institute of Technology; an honorary Doctor of Laws degree from Princeton University; and an honorary Doctor of Human Letters from Rutgers University. Dr. Vagelos is a Director of the Prudential Insurance Company of America, PepsiCo, Inc., McDonnell Douglas Corporation, and the Estee Lauder Companies, Inc. He also is the Chairman of the board of Trustees of the University of Pennsylvania and a Trustee of The Danforth Foundation.

Richard J. Whitley, M.D., Clinical Trials Area Review Panel Chair, is the Loeb Eminent Scholar Chair in Pediatrics, Vice Chairman in the Department of Pediatrics, Associate Director in the Center for AIDS Research, and a Scientist in the Cancer Research and Training Center at the University of Alabama at Birmingham. His numerous awards and honors include membership in the Society for Pediatric Research, the Infectious Diseases Society, and the 1991 Award for Excellence in Pediatric Research by the American Academy of Pediatrics. In 1991, he also was named to be the Canon Ely Lecturer at the Harvard School of Medicine, Children's Hospital, in Boston, Massachusetts. His many professional memberships include the American Society for Microbiology, the American Society for Virology, the Pediatric Infectious Diseases Society, and the International Society for Antiviral Research. Dr. Whitley has served on numerous national and international committees, including several NIH committees. He has made significant contributions to the scientific literature and has produced an exhaustive list of more

than 370 journal articles, book chapters, editorials, and abstracts, in addition to editing and co-editing several important medical books on infections and viral diseases.

David Baltimore, Ph.D., is the American Cancer Research Professor, the Ivan R. Cottrell Professor of Molecular Biology and Immunology, and Institute Professor at the Massachusetts Institute of Technology. He is a member of the Office of AIDS Research Advisory Council (OARAC), the Board of Directors of the Dibner Institute for the History of Science and Technology, and the Scientific Advisory Committee at Children's Hospital. He has served on the ad hoc committee to review the National Cancer Institute, and on the basic research subcommittee of the NIAID AIDS Research Advisory Committee. He also has served as the Chairman of the Board of Trustees at the Scientists Institute for Public Information, and has been a member of the Hewlett-Packard Laboratories Research Board and its Board of Governors in addition to being a member of the AIDS Oversight Committee of the Institute of Medicine and the Scientific Advisory Board of the Massachusetts General Hospital Cancer Center. Dr. Baltimore is an internationally known researcher with a bibliography of over 500 scientific publications. He has been elected a member of the American Academy of Arts and Sciences, the Pontifical Academy of Sciences, the American Medical Writers Association, Foreign Member, The Royal Society, the Institute of Medicine, the Japanese Biochemical Society, and the American Academy of Microbiology. In 1975, he received the Nobel Prize in Physiology or Medicine.

Appendix B

AREA REVIEW PANEL MEMBERS

Natural History, Epidemiology, and Prevention Research Area Review Panel

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Appendix D

GLOSSARY

ABL	Applied BioScience Laboratories
ACTG	AIDS Clinical Trials Group, NIAID
ACTU	AIDS Clinical Trials Unit
ADC	AIDS Dementia Complex
Add-HEALTH	National Longitudinal Study of Adolescent Health, funded by NICHD
AHCPR	Agency for Health Care Policy Research, DHHS
AIDS	Acquired Immunodeficiency Syndrome
AITRP	AIDS International Training and Research Program, FIC
AMC	AIDS Malignancy Consortium, NCI
ARAC	AIDS Research Advisory Committee, NIAID
ARC	AIDS-Related Complex
ARIS	AIDS Research Information System, an OAR database
ARP	Area Review Panel
ARR	AIDS-related research
AVEG	AIDS Vaccine Evaluation Group
AZT	zidovudine (generic name) or azidothymidine
APCs	antigen presenting cells
Bishop-Calabresi Report	"A Review of the Intramural Program of the National Cancer Institute," a report by the Ad Hoc Working Group of the National Cancer Advisory Board, dated June 26, 1995, co-chaired by J. Michael Bishop, M.D., and Paul Calabresi, M.D.

BIV	Bovine Immunodeficiency Virus
BSSR	Behavioral, Social Science and Prevention Research
BTDP	Behavioral Therapies Development Program, NIDA
CAB	Community Advisory Board
CAIR	Center for AIDS Intervention Research at the Medical College of Wisconsin
CAM	complementary and alternative medicine
CAPS	Center for AIDS Prevention Studies, UCSF (funded by NIMH)
Cassell-Marks Report	"Report of the Extramural Advisory Committee of the Director's Advisory Committee and the Implementation and Progress Report," Intramural Research Program, NIH, November 17, 1994, co-chaired by Gail H. Cassell, Ph.D., and Paul A. Marks, M.D.
Cassman Report	"Report of the Working Group on the Division of Research Grants," chaired by Marvin Cassman, Ph.D., issued May 1995
CC	Clinical Center, NIH
CDC	Centers for Disease Control and Prevention, DHHS
CIL	Central Immunology Laboratory
CMI	Cell-mediated immunity
CMIG	Collaborative Mucosal Immunology Groups
CMV	cytomegalovirus, a herpes virus, an OI
CNS	central nervous system
COGS	Cooperative Oncology Groups (COGs), NCI
Cohort	a group of individuals with some characteristics in common
CPCRA	Terry Beirn Community Programs for Clinical Research on AIDS, NIAID
CRISP	Computer Retrieval Information Systems Program, a DRG data base
CTEP	Clinical Therapeutics Evaluation Program, NCI

CTL	cytotoxic T lymphocytes
DAIDS	Division of AIDS, NIAID
DASH	Division of Adolescent School Health, CDC
DATRI	Division of AIDS Treatment Research Initiative, NIAID
DCRT	Division of Computer Research and Technology, NIH
ddC	dideoxycytidine, a cytidine nucleoside analogue
ddI	didanosine, a purine nucleoside analogue
DHHS	Department of Health and Human Services
DMC	Domestic Master Contractor for domestic HIV/AIDS vaccine efficacy trials, NIAID
DoD	Department of Defense
DRG	Division of Research Grants, NIH
DSMB	Data Safety and Monitoring Board
DSPN	distal motor polyneuropathy
DTP	Developmental Therapeutics Program, NCI
EEC	European Economic Community
EBV	Epstein-Barr Virus
FDA	Food and Drug Administration, DHHS
FCRDC	Frederick Cancer Research and Development Center, NCI
FCRF	Frederick Cancer Research Facility
FIC	Fogarty International Center
FIRCA	Fogarty International Research Collaboration Awards, FIC
FIRST	First Independent Research Support and Transition Award, (R29)
FIV	Feline Immunodeficiency Virus, also FeLV

GCRC	General Clinical Research Centers, NCRR
GI	gastrointestinal
HIV-1	Human Immunodeficiency Virus Type 1
HIV+	HIV-infected
HIVNET	HIV Vaccine Efficacy Trials Network, a network of domestic and international sites for trials of various prevention strategies, NIAID
HHMI	Howard Hughes Medical Institute
HLA	Human Leukocyte Antigen (Histocompatibility Antigen)
HPV	Human papilloma virus
HRSA	Health Resources and Services Administration
HuSCID	severe combined immunodeficiency mice strain transplanted with human immune tissue
ICD	Institutes, Centers, and Divisions [of NIH]
IDU	Injection Drug Use, Injection Drug User
IMC	International Master Contract for HIVNET
IND	investigational new drug
INT	HIV integrase
IOM	Institute of Medicine, National Academy of Science
IRG	Initial Review Groups: study sections within DRG
IRP	Intramural Research Program ICDs
KS	Kaposi's Sarcoma
KSHV	Kaposi's Sarcoma Herpes Virus
LCMV	lymphocytic choriomeningitis virus
MACS	Multicenter AIDS Cohort Study, NIAID
MAIDS	Murine acquired immunodeficiency syndrome

MESH	Medical Subject Headings
MIRT	Minority Investigator Research Training, NIH
MSM	Men who have sex with men
NADR	National AIDS Demonstration Research and Cooperation Agreement at NIDA
NARAC	NIAID AIDS Research Advisory Committee
NARC	Neurologic AIDS Research Consortium, NINDS
NAVTF	National AIDS Vaccine Task Force (proposed)
NCDDG	National Cooperative Drug Discovery Groups
NCHGR	National Center for Human Genome Research, NIH
NCI	National Cancer Institute, NIH
NCRR	National Center for Research Resources, NIH
NCVDG	National Cooperative Vaccine Development Groups, NIAID
NEI	National Eye Institute, NIH
NEP	needle/syringe exchange programs
Neuro-AIDS	neurological manifestations of HIV infection
NHEBP	Natural History, Epidemiology, and Biomedical Prevention [Area Review Panel]
NHLBI	National Heart, Lung, and Blood Institute, NIH
NIA	National Institute on Aging, NIH
NIAAA	National Institute on Alcohol Abuse and Alcoholism, NIH
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH
NICHD	National Institute of Child Health and Human Development, NIH
NIDA	National Institute on Drug Abuse, NIH
NIDCD	National Institute on Deafness and Other Communication Disorders, NIH

NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases, NIH
NIDR	National Institute of Dental Research, NIH
NIEHS	National Institute of Environmental Health Sciences, NIH
NIGMS	National Institute of General Medical Sciences, NIH
NIH	National Institutes of Health
NIMH	National Institute of Mental Health, NIH
NINDS	National Institute of Neurological Disorders and Stroke, NIH
NINR	National Institute on Nursing Research, NIH
NK	Natural Killer cells (of the immune system)
NLM	National Library of Medicine, NIH
NMR	nuclear magnetic resonance
NO	nitrous oxide
OAR	Office of AIDS Research, NIH
OAM	Office of Alternative Medicine, NIH
OBSSR	Office of Behavioral, Social Science, and Prevention Research, NIH
OD	Office of the Director, NIH
OI	opportunistic infection
OT	opportunistic tumor (also OM, opportunistic malignancy)
PACTG	Pediatric ACTG, NIAID
PAHO	Pan American Health Organization
PBMC	peripheral blood mononuclear cells
PCP	*Pneumocystis carinii* pneumonia
PCR	polymerase chain reaction
PHS	Public Health Service, DHHS

PI	principal investigator
PML	Progressive Multifocal Leukoencephalopathy, an OI
PNS	peripheral nervous system
PROG	peer-review oversight group
RCT	randomized clinical trials
RFA	Request for Applications (R01 mechanism, or cooperative agreements)
RFP	Request for Proposals (N01 mechanism, contract)
R01	investigator-initiated award (R01 grant)
R29	see FIRST
RPG	Research Program Grants, issued from NIH
RPRC	Regional Primate Research Centers, NCRR
RT	reverse transcriptase, a retroviral enzyme
SAIC	Science Applications International Corporation
SAMHSA	Substance Abuse, Mental Health Services Administration, DHHS
SBIR	Small Business Innovative Research program, NIH
SCID	severe combined immunodeficiency mice
SHIV	a chimera of SIV and HIV-1
SIV	simian immunodeficiency virus
SOCA	Studies of the Ocular Complications of AIDS, NEI
SPF-macaque	specific pathogen free macaque
SPIRAT	Strategic Program for Innovative Research on AIDS Therapies, NIAID
STD	sexually transmitted disease
STTR	Small Business Technology Transfer programs, NIH
3TC	lamivudine

TB	tuberculosis
UCSD	University of California at San Diego
UCSF	University of California at San Francisco
VRDARP	Vaccine Research and Development Area Review Panel
WHO	World Health Organization
WIHS	Women's Interagency HIV Study, funded by NIAID, NICHD, and other ICDs
WITS	Women and Infants Transmission Study, NIAID
WRAIR	Walter Reed Army Institute of Research, DoD